



Docket No.: 273802002200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jacob Sten PETERSEN

Application No.: 09/064,682

Group Art Unit: 1645

Filed: April 22, 1998

Examiner: R. Swartz

For: COMBINATIONS OF ANTIGEN AND
MUCOSAL BINDING COMPONENTS FOR
INDUCING SPECIFIC IMMUNOLOGICAL
TOLERANCE

#33
JM
9/1/03

**DECLARATION OF CECIL CZERKINSKY
PURSUANT TO 37 C.F.R. § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Cecil Czerkinsky, hereby declare as follows:

1. I am the Director of the National Institutes of Health and Medical Research, Laboratory of Mucosal Immunity and Vaccinology, University of Nice-Sophia Antipolis, School of Medicine, Nice France. I have published more than 120 papers including reviews in the field of experimental medicine, and especially in the areas of vaccinology and mucosal immunology. I have been the guest speaker and/or chairperson at nearly 100 international conferences and symposia. Other details of my credentials are listed in my curriculum vitae, which is attached as Exhibit 2.

2. I have been asked to provide my opinion regarding the above-referenced patent application by Dr. Jacob Sten Petersen, the inventor of the above-referenced patent application. I have been given the Specification and the Office Action dated January 2003 as well as the documents referred to by the U.S. patent examiner.

3. The Examiner states that it would have been obvious to one skilled in the art that administration of CTB and antigen by the oral route would induce tolerance to the antigen in view of Tsuru (JP 3109328) and of Elson ("Elson"; Current Topics Microbiology 1999, 146:29-33). Having myself been fairly active in this area, I cannot agree with the Examiner's argument because (i) neither Elson nor Tsuru teach that CTB and an antigen given by a mucosal route can induce specific tolerance to said antigen, and (ii) because oral administration of CTB per se has never been shown to induce tolerance.

4. Elson teaches that cholera toxin B subunit can serve as a mucosal adjuvant when co-administered with an antigen. In another study, Elson has shown that although feeding a protein antigen alone did induce oral tolerance, CT feeding did not induce oral tolerance and the feeding of the B subunit of CT did not result in oral tolerance either (Elson and Ealding, J. Immunol. 1984 Dec;133(6):2892-7) (Attachment 5). Dr. Petersen, in the instant specification, teaches that, contrary to Elson and others, mucosal administration of recombinant CTB administered together with an antigen induces immune suppression (oral tolerance) to said antigen. Clearly, it was not obvious to one skilled in the art to have predicted such effects from the teaching of Elson.

5. Further, the Examiner contends that the specification does not teach "specific" tolerance to one antigen and that the effects observed by Petersen could have resulted from the

induction of a phenomenon of general (non specific) tolerance by CTB as taught by Tsuru (JP 3109328). It is clear that such non specific tolerance has been documented for cholera toxin and anticipated for cholera toxin B subunit given by a non mucosal, i.e., a systemic (intravenous, intramuscular) route. Again, this is largely because these molecules have been shown to be directly toxic on certain lymphocyte subsets (CD8+ cytotoxic T cells) which are known to play a critical role in graft rejection.

6. In fact, it is well known in the art that the induction of mucosally induced systemic tolerance or so-called "oral tolerance" is antigen-specific (Czerkinsky et al, Immunol Rev. 1999 Aug;170:197-222. Review) (Attachment 6). The results presented in the specification are consistent with this notion since mucosal administration of CTB alone did not per se affect the development of the autoimmune response to pancreas autoantigens resulting in diabetes nor to parenterally injected tetanus toxoid as one would have expected it from a non specific immunosuppressive compound. Thus, when given by a mucosal (oral) route as opposed to a non-mucosal route (e.g. intravenous, intraperitoneal, intramuscular), CTB behaves very differently and one could not have predicted the findings of Petersen from the teachings of Elson and Tsuru (JP 3109328).

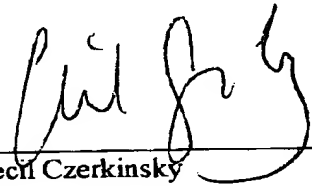
7. In conclusion, I regard the findings of Petersen as presented in the specification as unpredictable from the teachings of Elson and Tsuru and rather unexpected since immunological tolerance induced by mucosal co-administration of CTB and an antigen has previously (and obviously erroneously) been shown to require physical association of both compounds to be effective (Sun et al 1994, Proc. Natl Acad Sci USA 91:10795) (Attachment 4).

Application No.: 09/064,682

4

Docket No.: 273802002200

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: July 11, 2003
Cecil Czerkinsky